MYC Rearranged Aggressive B-Cell Lymphomas: A Report on 100 Patients of the Fondazione Italiana Linfomi (FIL)

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Advances in the classification of diffuse large B cell lymphoma (DLBCL) based on genetic aberrations and molecular expression profiles have led to the recognition of a new category of high grade B cell lymphoma, including "high grade B-cell lymphoma with rearrangements of MYC and BCL2 and/or BCL6", in the 2016 revised 4th edition of World Health Organization (WHO) Classification of Tumors of Haematopoietic and Lymphoid Tissues.[1]

The poor results achieved with R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) in multiple studies, have prompted the use of intensive treatments, such as Burkitt lymphoma regimens, stem-cell transplantation or dose-adjusted EPOCH-R (DA-EPOCH-R)[2–6] as first line treatments, even if no prospective comparisons are available.

On these bases we performed a "real life" retrospective multicenter study with the aim of characterizing the clinical and pathological landscape of MYC rearranged aggressive B-cell lymphomas in Italy, and comparing for efficacy the preferred therapeutic choices.

In the years 2011 to 2017, a total of 100 patients with newly diagnosed DLBCL (n = 65) or B cell lymphoma, unclassifiable (BCLU, n = 35) were collected from 29 Italian centers of the Fondazione Italiana Linfomi (FIL) Fig. S1 (Supplemental Digital Content, http://links.lww.com/HS/A49). Pathological data were retrieved from centrally reviewed local pathological reports. FISH (*fluorescent in-situ hybridization*) analysis was performed with current standard methods.[7]

Treatment groups were classified as follows: 1) "intensive regimens": incorporating high dose methotrexate: R-CODOX-M/IVAC [Rituximab, Cyclophosphamide, Oncovin (Vincristine), Doxorubicin, Methotrexate alternating with Rituximab, Ifosfamide, Vepesid (etoposide), Ara-C (Cytarabine)], n = 23, GMALL-R (German Multicenter Study Group for the Treatment of Adult Acute Lymphoblastic Leukemia, Rituximab), n = 9, R-Hyper-CVAD/R-MA [Rituximab, Hyperfractionated Cyclophosphamide, Vincristine, Adriamycin (Doxorubicin), Dexamethasone alternating with Rituximab, Methotrexate, Ara-C (Cytabine)], n = 10; 2) "R-CHOP-like": including also R-COMP, n = 6 (R-CHOP with liposomal anthracycline), R-miniCHOP, n = 2, R-M/VACOP-B (Rituximab, Methotrexate/Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Prednisone, and Bleomycin), n = 2, R-mega-CHOP, n = 1; 3) "DA-EPOCH-R": dose-Adjusted Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Prednisone and Rituximab. Patients treated with different approaches or palliative care ("others") were censored for survival analysis, or analyzed separately.

The primary end-point was progression-free survival (PFS), defined as the time between lymphoma diagnosis and relapse or progression, lack of response, or death from any cause. Survival curves were estimated using the Kaplan-Meier product limit method. Statistical analyses were performed using the Stata 13.0 software (Stata Corp., College Station, TX).

All 100 patients presented MYC rearrangement as for inclusion criteria, 57 patients were double hit for BCL2 (DHL-BCL2) and 29 were double hit for BCL6 (DHL-BCL6). The remaining 19 MYC rearranged patients, lacking an additional BCL2 or BCL6 translocation, were defined single hit lymphomas (SHL – MYC+/BCL2-/BCL6-). Five patients carried all the three rearrangements, so called "triple hit lymphoma" (THL – MYC+/BCL2+/BCL6+) and for survival analysis were considered among DHLs.

Clinical and pathological features of the whole series are detailed in Table 1. Eight patients had central nervous system (CNS) involvement at diagnosis (2 parenchymal, 6 meningeal).

Patient and Tumor Characteristics.

Features	MYC rearranged (n = 100)	SHL (n = 19)	DHL and THL (n = 81)[a]	p value
Median age, range	61, 19-85	62, 19-80	61, 21-85	0.4
Male sex	62 (62%)	10 (53%)	52 (64%)	0.2
B symptoms	37 (37%)	6 (32%)	31 (38%)	0.3
AAS III-IV	82 (82%)	12 (63%)	70 (86%)	0.02
Elevated LDH	73 (73%)	10 (53%)	63 (77%)	0.03
ECOG PS ≥2	36 (36%)	5 (26%)	31 (38%)	0.2
Extranodal sites ≥ 2	42 (42%)	6 (32%)	36 (44%)	0.2
Bone marrow involvement	35 (35%)	4 (21%)	31 (38%)	0.1
Bulky > =6 cm	59 (59%)	8 (42%)	51 (62%)	0.08
CNS involvement	8 (8%)	1 (5%)	7 (8%)	0.5
IPI risk group				
good (0)	1 (1%)	1 (5%)	0	
intermediate (1–2)	35 (35%)	10 (53%)	25 (31%)	0.02
poor (3–4–5)	64 (64%)	8 (42%)	56 (69%)	
Histology				
DLBCL NOS	65 (65%)	13 (68%)	52 (64%)	0.4
BCLU	35 (35%)	6 (32%)	29 (36%)	
Cell-of-origin by Hans[b]				
GCB	67 (67%)	12 (63%)	55 (67%)	0.5
non-GCB	18 (18%)	4 (21%)	14 (17%)	
Translocations				NA
MYC	100	19	81	
BCL2	57	0	57 (70%)	
BCL6	29	0	29 (35%)	

DHL = double hit lymphomas; includes: [(MYC+/BCL2+/BCL6-), DHL-BCL2]; [(MYC+/BCL2-/BCL6+), DHL-BCL6].

SHL = single hit lymphomas (MYC+/BCL2-/BCL6-). AAS = Ann Arbor stage, BCLU = "unclassifiable" aggressive B-cell lymphoma, CNS = central nervous system, DLBCL NOS = Diffuse large B cell lymphoma not otherwise specified, ECOG PS = Eastern Cooperative Oncology Group performance status, GCB = Germinal Center B-Cell like, IPI = International Prognostic Index score, LDH = lactate dehydrogenase, NA = not applicable.

[a] 5 of them presented a concomitant rearrangement of both MYC and BCL2 and BCL6 (MYC+/BCL2+/BCL6+), the so called triple hit lymphomas (THL).

[b] Not done in 15 patients.

The majority of patients (n = 42) were treated upfront with intensive schedules, followed by R-CHOP like (n = 35) and by DA-EPOCH-R (n = 18). Five patients were treated with other schemes (Supplementary Table S1, Supplemental Digital Content, http://links.lww.com/HS/A49). Eighteen patients received ASCT consolidation. Overall, 70 patients received CNS prophylaxis: intrathecal in 24, systemic MTX in 8, and both in 38. Finally, 20 patients received radiotherapy consolidation. Patients treated with intensive regimens presented with similar baseline features to patients treated with R-CHOP, with exception of more advanced IPI in intensive group (p = 0.006), and similar to DA-EPOCH-R group, with the exception of higher ki67 values (p = 0.04), and advanced stage (p = 0.02). Finally, patients presenting a BCLU histology received more frequently intensive treatment than standard R-CHOP or DA-EPOCH-R, p = 0.001 and p = 0.05, respectively, (Supplementary Table S2, Supplemental Digital Content, http://links.lww.com/HS/A49).

Overall response was 71%, with 58 patients achieving complete response (CR) and 13 partial response (PR) at the end of front-line treatment. Three patients died of treatment related complications (infections) during induction, and one did not receive any treatment. CR rate was 68% in SHL and 56% in DHL (p = 0.2), see Supplementary Table S2 (Supplemental Digital Content, http://links.lww.com/HS/A49). Patients treated with intensive schedules had a CR of 69% (29/42), which was not statistically different from patients treated with R-CHOP (18/35, 51%, p = 0.08), and similar to patients treated with DA-EPOCH-R (11/18, 61%, p = 0.4).

After a median follow up for survivors of 33 months, the 24 months PFS and OS of the overall MYC rearranged (MYC-R) population were 54% (95% CI 44–63) and 57% (95% CI 46–66), respectively, Fig. S2A and Fig. S2B (Supplemental Digital Content, http://links.lww.com/HS/A49). For the 19 patients with SHL and the 81 patients with DHL, PFS at 24 months was 77% (95% CI 51–91) and 49% (95% CI 37–59), respectively (p = 0.05), Fig. S2C (Supplemental Digital Content, http://links.lww.com/HS/A49), and OS was 77% (95% CI 50–90) vs 52% (95% CI 40–63), respectively (p = 0.1), Fig. S2D. http://links.lww.com/HS/A49 PFS did not vary significantly based on the specific double rearrangements found (ie, DHL-BCL2 vs DHL-BCL6 vs THL), Fig. S3 (Supplemental Digital Content, http://links.lww.com/HS/A49).

Analyzing all the MYC-R population, the 24 months PFS was 59% (95% CI 33–78) in patients treated with DA-EPOCH-R (p = 0.6, compared with intensive treatments), 46% (95% CI 29–62) in those receiving R-CHOP-like schedules (p = 0.04), and 65% (95% CI 49–68) in patients who received intensive treatments, Fig. 1. In the same population, the 24 months OS was 74% (95% CI 45–89) in patients treated with DA-EPOCH-R, which was superior to patients receiving R-CHOP-like schedules, 46% (95% CI 27–62), p = 0.05. However, no significant OS difference was seen between DA-EPOCH-R and intensive regimens. Moreover, restricting the analysis to the group of elderly patients (age > 65 years, n = 42), no survival advantage was observed in patients treated with DA-EPOCH-R or intensive regimens vs R-CHOP-like. Superimposable results were obtained selecting the 81 DHL patients only, with a PFS and OS advantage for patients receiving DA-EPOCH-R and intensive regimens vs R-CHOP-like (p = 0.02), Fig. S4 (Supplemental Digital Content, http://links.lww.com/HS/A49). 24 months OS in the 81 DHL patients was 66% (95% CI 33–86) for DA-EPOCH-R, 34% (95% CI 15–53) for R-CHOP-like (p = 0.03
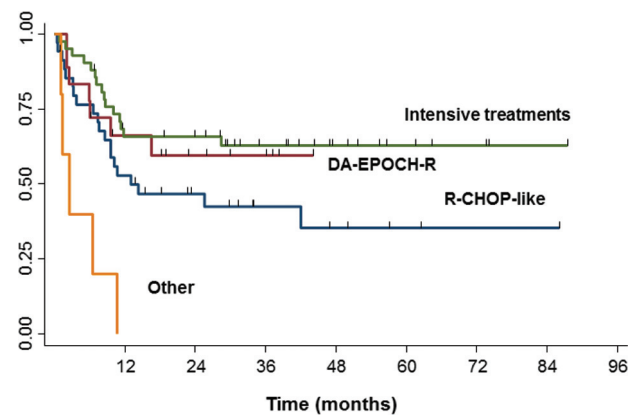

Figure 1. PFS by delivered treatment: 24 months PFS 65% (95% CI 49–68) in patients who received intensive treatments, 46% (95% CI 29–62) in those who received R-CHOP-like schedules (p = 0.04 compared with intensive and DA-EPOCH-R); 59% (95% CI 33–78) in patients treated with DA-EPOCH-R (p = 0.6, compared with intensive treatments) and not evaluable in patients treated with other treatments (p = 0.001).

and p = 0.05 respectively), and 64% (95% CI 46–77) for intensive treatments.

ASCT consolidation (n = 18) did not give any PFS advantage in patients achieving CR or PR at the end of induction treatment (p = 0.3 and 0.4, respectively), Fig. S5A and Fig. S5B (Supplemental Digital Content, http://links.lww.com/HS/A49). Actually, patients in CR at the end of induction retained a good 24 months PFS even without ASCT (82%–95% CI 69–90).

Moreover, despite quite aggressive CNS prophylaxis, 5/100 patients experienced a CNS relapse during observation period (two of them presenting a CNS involvement already at diagnosis). Finally, the outcome after relapse was very poor, accounting for a 24 months OS of 13% (95% CI 4–24), Fig. S6 (Supplemental Digital Content, http://links.lww.com/HS/A49).

In the overall MYC-R population, B-symptoms (p = 0.05), ECOG performance score (PS) > 2 (p = 0.003), bone marrow infiltration (p = 0.005), elevated LDH levels (p = 0.03) and poor risk IPIaa (p = 0.05), predicted worse PFS (Supplementary Table S3, Supplemental Digital Content, http://links.lww.com/HS/A49). Restricting analysis for DHL population, only ECOG PS > 2 (p = 0.01) and bone marrow infiltration (p = 0.05) retained their prognostic impact. Finally, after Cox proportional hazard multivariate analysis, only a poor ECOG (> 2) remained predictive of poor PFS, p = 0.009 (95% CI 1.21–3.86), HR 2.16.

Overall, the main results of this study can be summarized as follows:

1) "High-grade B-cell lymphoma with MYC and BCL2/BCL6 rearrangements" show an overall worse prognosis than "single-hit" MYC-R patients in terms of PFS;
2) frontline intensive chemotherapy and DA-EPOCH-R are associated with a significant survival benefit if compared with R-CHOP-like treatments;
3) restricting the analysis to the group of elderly patients, the advantage for intensive regimens was no longer observed, suggesting that younger patients might benefit the most from these schedules;
4) survival is not significantly impacted by ASCT consolidation, regardless of the clinical response observed;

5) survival after progression in "high-grade B-cell lymphoma with MYC and BCL2/BCL6 rearrangements" is particularly dismal, suggesting that salvage therapies are ineffective in this setting.

Therefore, with the limits of a retrospective series, we reported a large, National, homogeneous population, where the distribution of the baseline characteristics and the clinical results are very similar to those of previously published unselected cohorts[2,8,9] As regards CNS relapse, its cumulative incidence was inferior to that of the MDACC retrospective cohort[8] (5% at 2 years vs 13% at 3 years). Even if the numbers are too small to drive sound correlations between the received prophylaxis (intrathecal vs systemic) and the characteristics of CNS relapse (meningeal vs parenchimal), this difference might be due to a more aggressive upfront CNS prophylaxis in our series. Finally, as screening of all DLBCL and BCLU cases for MYC rearrangement was not the routine practice of all participating centers, we cannot exclude the possibility that selection bias influenced the decision to test specific cases.

In conclusion, the results of our study confirm that R-CHOP is not an appropriate therapeutic choice for "high-grade B-cell lymphoma with MYC and BCL2/BCL6 rearrangements", and that intensive regimens or DA-EPOCH-R should be preferred, especially for younger patients. Nevertheless, the current diagnostic work-up of aggressive B cell lymphomas is controversial, and the screening strategy to drive FISH testing is not clearly shared.[10-12] Moreover, the complex biological landscape of DLBCL probably cannot be simply resumed by classical FISH or cell of origin analysis: actually, new biological insights, including high-throughput mutational[13,14] and microenvironmental studies,[15] are needed for a better classification and a more effective testing of front line targeted agents.

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